Journal of Applied Research on Children: Informing Policy for Children at Risk

Volume 4
Issue 2 *Accountable Communities: Healthier Neighborhoods, Healthier Children*

Article 10

2013

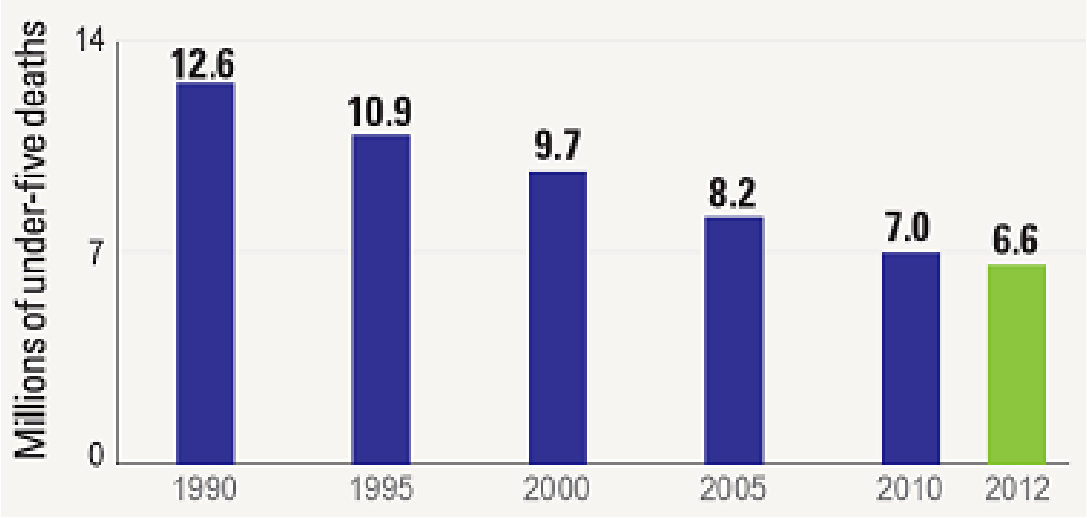
Pediatric Tropical Diseases and the World's Children Living in Extreme Poverty

Peter J. Hotez
Baylor College of Medicine, hotez@bcm.edu

Introduction: What Kills Children?

In a report released in September 2013, the United Nations Children's Fund (UNICEF), together with the World Health Organization (WHO) and World Bank identified substantial progress in reducing the number of children who die before their fifth birthday.[1] In the more than 20 years between 1990 and 2012 the number of such deaths worldwide has decreased from 12.6 million to 6.6 million (Figure 1), almost a 50% drop, with approximately one-half of the these deaths occurring in just five countries – three in Asia, India, Pakistan and China, and two in Sub-Saharan Africa, Democratic Republic of Congo and Nigeria.[1]

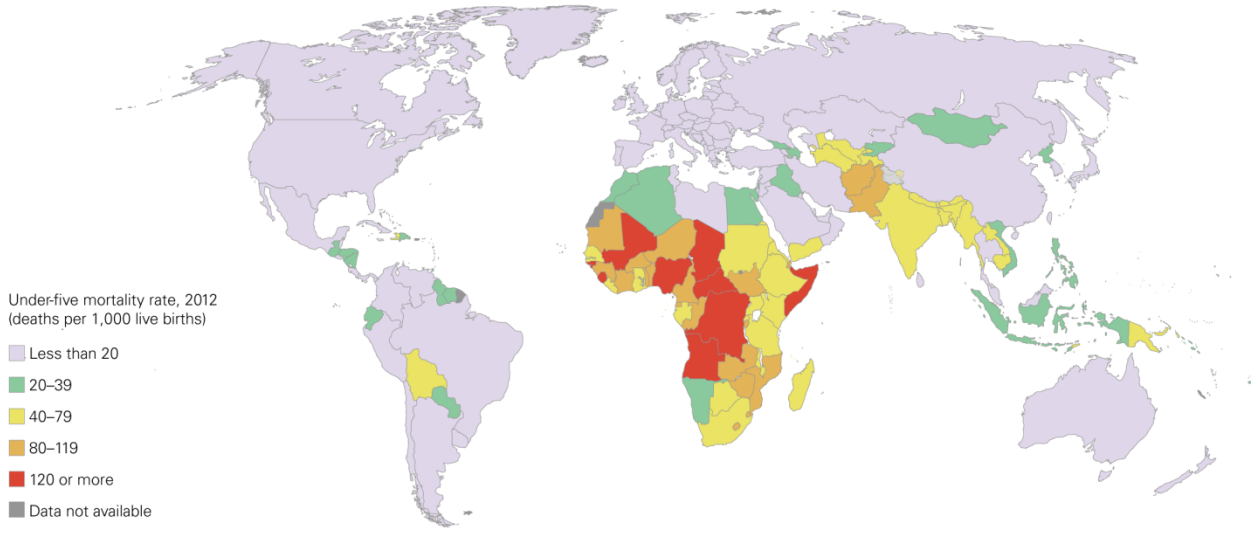
Figure 1. Decline in under-five child mortality since 1990. UNICEF analysis based on the United Nations Inter-agency Group for Child Mortality Estimation (IGME), Levels and Trends in Child Mortality: Report 2013, UNICEF, New York, 2013.



A key factor in the dramatic gains in reducing child mortality over the last two decades has been an increase both in the delivery of existing vaccines and the development of new vaccines. With regards to enhanced delivery, there has been a huge increase in the number of infants who receive their childhood vaccines, especially measles vaccine (with a 74% reduction in global measles deaths) and Hib (*Haemophilus influenzae* type B) vaccine,[2] while in parallel new vaccines for pneumococcal pneumonia and rotavirus diarrhea have been developed. A major organization in promoting these vaccines both for delivery and development has been the GAVI Alliance (formerly Global Alliance for Vaccines and Immunisation) –

a partnership of WHO, UNICEF, World Bank, the Bill & Melinda Gates Foundation, donor governments, developing countries, and international finance agencies, which was launched in January 2000 in order to fund vaccines for children in the world's 70 poorest countries.[3] Approximately 2.5 million children's lives may be saved annually through these activities.[2] If we look at what still kills under-five children today, mostly in developing countries in Sub-Saharan Africa, South and Southeast Asia, and a few of the poorest Latin American countries (Figure 2), almost one-half of the deaths occurs during the neonatal period (first 28 days of life) especially from pre-term birth and intrapartum-related complications. However, approximately 1.5 million children still die (before their fifth birthday) annually from vaccine-preventable diseases.[2] In response, in 2010 the Bill & Melinda Gates Foundation helped to launch the Decade of Vaccine (DoV) collaboration to expand political commitment for the use of vaccines and financing of immunization services, creating market incentives to ensure a reliable supply of affordable vaccines, and fostering a scientific infrastructure for producing vaccines that target high priority diseases.[2] Such activities are expected to produce important additional gains in the reduction in childhood deaths.

Figure 2. Global map of under-five childhood mortality rates in 2012, UNICEF analysis based on the United Nations Inter-agency Group for Child Mortality Estimation (IGME), Levels and Trends in Child Mortality: Report 2013, UNICEF, New York, 2013. (note: this map is stylized and not to scale. It does not reflect a position by UN IGME agencies on the legal status of any country or territory or the delimitation of any frontiers.)



Lagging Behind: The Pediatric Tropical Diseases

In contrast to the gains resulting from the GAVI Alliance and the DoV, with a few exceptions the overall prevalence of the leading tropical diseases of children such as dengue, malaria, schistosomiasis, soil-transmitted helminth infections, trachoma, and visceral leishmaniasis has not substantially decreased over the last twenty years, and in some cases may even be increasing. Shown in Table 1 are the major pediatric tropical infections ranked by the estimated number of cases, together with the number of deaths that result from these conditions and the number of disability-adjusted life years (DALYs), a metric that considers both the number of years of life lost from premature death and years lost through disability.[4-12] DALYs are an important metric for pediatric tropical diseases because many of them are not major killers, so much as important disablers affecting child development, fitness, future intelligence, and wage earning. Below Table 1 is a brief summary of the major pediatric tropical diseases.

Table 1. Leading Tropical Infections that Disproportionately Affect Children Ranked by number of estimated cases, DALYs, Deaths

Disease	Estimated no. cases	DALYs	Deaths	Reference
Soil-transmitted helminth infections	890 million	5.2 million	2,700	5-8
Dengue	390 million	0.8 million	14,700	5-7, 9
Malaria	216 million	82.7 million	655,000-1,169,500	5-7, 10
Schistosomiasis	207 million	3.3 million	11,700	5-7, 11
Trachoma	21 million	0.3 million	0	5-7, 12
Visceral leishmaniasis	0.2-0.4 million	3.3 million	51,600	5-7, 13
Total	1.7 billion	95.6 million	735,700-1,250,200	

*With the exception of the children who require treatment for soil-transmitted helminth infections these numbers reflect both adults and children although children account for majority of the disease burden.

Soil-transmitted helminth (STH) infections. STH infections include ascariasis – roundworm infection, trichuriasis – whipworm infection, and hookworm infection. Although they are not killer diseases, these intestinal nematode infections disproportionately affect preschool and school-aged children, leading to growth stunting and intellectual and cognitive delays, and even reductions in future economic potential.[7,13-16] The WHO currently estimates that more than 800 million children, a large percentage of children in developing countries, require annual anthelminthic treatments – deworming.[7] STH infections are widely prevalent wherever rural poverty intersects tropical climates in Africa, South and Southeast Asia, and Latin America.[13]

Dengue. Dengue fever is a flavivirus infection transmitted by *Aedes* mosquitoes that causes high fever, headache, rash, and joint pain, and in severe cases leads to hemorrhage, shock, and death.[16] Children tend to suffer from the greatest morbidity and mortality.[16] There has been a huge increase in the number of dengue cases annually, with new estimates indicating that as many as 390 million cases occur. Among the factors contributing to the emergence of dengue are urbanization, environmental degradation, lack of mosquito control, increased air travel, and possibly climate change.[8,16] India and South Asia, the Pacific islands, and coastal Latin America, including Brazil and Central America, are currently experiencing some of the largest outbreaks of dengue.

Malaria. Malaria is a parasitic protozoan infection transmitted by *Anopheles* mosquitoes. It remains one of the great childhood killers, especially among children between the ages of six months and five years.[9,17] An estimated 216 malaria infections occur annually, and between 655,000 and 1.2 million people die annually from malaria, most of it caused by one species *Plasmodium falciparum,* with most of the deaths among children in Sub-Saharan Africa and India.[5,9]

Schistosomaisis. Schistosomaisis is another helminth infection caused by blood flukes (schistosomes) that frequently occurs together with STH infections in children.[10,18] Both STH infections and schistosomiasis result in childhood growth delays, but schistosomiasis also produces severe pathology to the urogenital tract and liver and intestines.[18] It has been estimated that 207 million cases occur annually with about 90% of the cases in Africa[10]; however, other investigators have suggested that the actual number could be much higher such that schistosomiasis ranks with STH infections as the most common tropical diseases.[18]

Trachoma. Trachoma is a chronic ocular infection caused by the intracellular bacteria *Chlamydia trachomitis*. It is a leading cause of blindness in low-income countries, especially in poor rural areas of Africa, Asia, and Central and South America, Australia, and the Middle East.[11,19] It is especially common in preschool children in areas where the infection is hyperendemic.[19] Approximately 21 million cases occur worldwide, of whom 2 million are visually impaired and one million are blind.[19]

Visceral Leishmaniasis (VL). VL is a systemic illness that affects the liver, spleen, and bone marrow (reticuloendothelial system) and is caused by parasitic intracellular protozoa of the genus *Leishmania*. Between 0.2 and 0.4 million cases of VL occur worldwide, but most of the new cases now occur in India (especially in Bihar State), Bangladesh, Sudan and South Sudan, Ethiopia, and Brazil.[12] The disease is associated with a high mortality unless treated promptly.

Assessing the toll

Overall, these six tropical infections exert a huge impact on child health, including more than 1.7 billion infections, almost 100 million DALYs, and between 700,000 and 1.2 million deaths. To put some of these numbers in perspective, the tropical diseases that disproportionately affect children cause more DALYs than HIV/AIDS,[5] and account for more than 10% of all childhood deaths. Moreover, it is common for a child to be affected by multiple tropical diseases at the same time. For instance, soil-transmitted helminth and schistosomiasis co-infections are common, as are these infections together with malaria or trachoma.[20] Dengue and malaria co-infections also occur.[21]

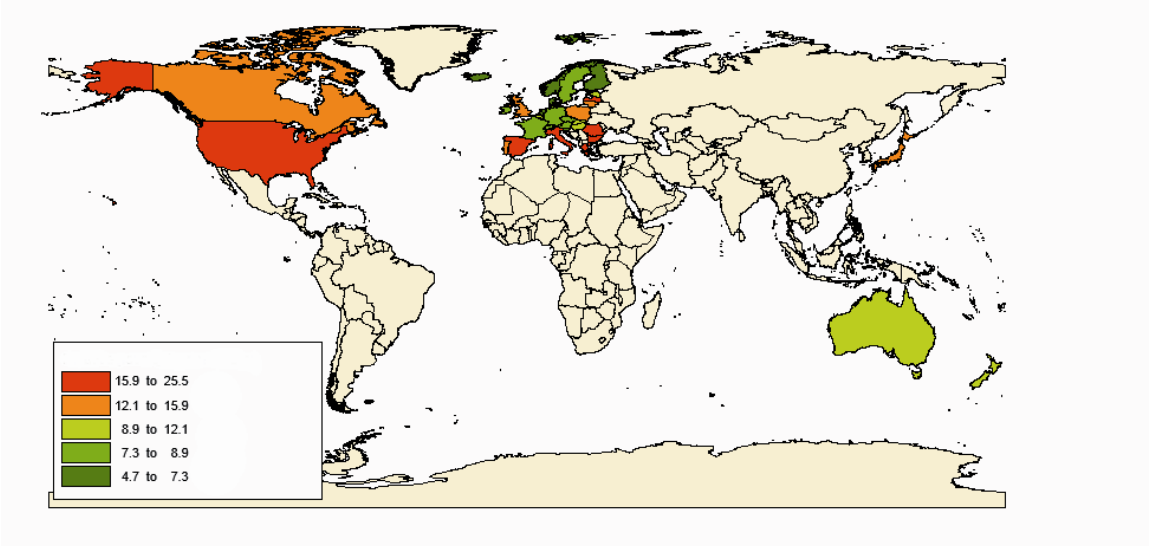
Even beyond the terrible health toll from tropical infections in childhood in terms of DALYs and deaths there is a potentially large socioeconomic impact. There is increasing recognition that poverty is an overriding determinant for these tropical diseases, and that these infections actually cause poverty.[22] Malaria was a key factor in thwarting economic growth in southern Europe during the mid-twentieth century,[23] while today STH infections, schistosomiasis, trachoma, VL, and dengue are holding back the economic development of Africa and Asia.[15,18,24-27] However, we are still at a relatively nascent stage of assigning specific dollars lost annually from tropical infections, and there is not yet detailed information on exactly how tropical diseases cause economic losses. Major factors include losses in agricultural productivity, deficits in child intellect and cognition, hospital and health care costs, and maternal illness.[22] Thus, while we call the six childhood infections “tropical,” they are first and foremost diseases of extreme poverty.

Consistent with the links between pediatric tropical infections and poverty is a recent finding that many of the world's tropical infections occur mostly among the extreme poor living in emerging economies of the group of 20 nations.[28] Of the 1.2 billion of the world's poorest people living below the World Bank poverty line of $1.25 per day,[29] approximately 50% live in G20 countries, led by India, China, Indonesia, and Brazil. Together these three countries account for more than 600 million people living in extreme poverty. Thus tropical infections such as VL, STH infections, lymphatic filariasis, food-borne trematodiases, leprosy, Chagas disease, and dengue disproportionately occur among the poor in G20 countries.[29]

Pediatric tropical diseases in the United States

To emphasize even further the poverty links is an emerging story of tropical diseases among the poor in the southern United States. More than 16 million children in the US (22% of all children) live in families living below the federal poverty level,[30] with approximately one-fifth of those children in rural poverty.[31] Of particular concern is the finding by the University of Michigan National Poverty Center that 1.65 million households with 3.55 million children live on less than $2 per person per day in a given month.[32] Thus sporadic pockets of poverty in the US approach levels seen in developing countries. As shown in Figure 3, the US ranks near the bottom of industrialized countries in terms of child poverty rates.[33]

Figure 3. Relative child poverty among industrialized nations by percentage. Map created using data from Unicef Inocenti Research Centre Report Card 10, Measuring Child Poverty.



Child poverty in the US is not evenly distributed; it disproportionately occurs in the southern states and among people of color, especially non-Hispanic black and Hispanic children.[34] We Identified several neglected tropical diseases affecting impoverished children in the Southern U.S., including parasitic infections such as toxocariasis, a larval helminth infection linked to pulmonary and neurological deficits and pathologies. [35-39] Other parasitic infections associated with child poverty include toxoplasmosis and cysticercosis, while impoverished adults were affected by trichomoniasis and Chagas disease.[35] A key tropical viral infection now found in the southern US is dengue, which is linked to poverty in South Texas,[35,40] while West Nile virus infection is associated with homelessness in Texas.[41] Indeed, probably the highest prevalence of these tropical infections occurs in Texas, where transmission of most of these diseases occurs (as opposed to importation through immigration).[42] So far two economic analyses of tropical infections in the US have been conducted.[43,44] The total costs of Chagas disease in the US approach $900 million annually,[43] while since 2002 West Nile virus infection cost $112 million in Texas alone.[44]

Combating tropical infections through disease control and prevention

There is not a unified global alliance to combat all the major tropical diseases of children, but there are pockets of success. One of the most promising enterprises for tropical disease control has been launched through joint efforts supported by the governments of the US and United Kingdom through their major overseas development organizations. Both governments are providing financial support to health ministries in Africa and elsewhere to implement mass treatments using packages of essential medicines that target several tropical infections affecting children, including the STH infections, schistosomiasis, and trachoma, in addition two parasitic infections of adults – lymphatic filariasis and onchocerciasis.[45,46] These treatments can be administered for only $0.50 per year, so that it is incredibly inexpensive and possibly as cost-effective as vaccines, and is leading to the elimination of lymphatic filariasis, onchocerciasis, and trachoma, while reducing the burden of disease from STH infections and schistosomiasis.[47] Currently effective programs for large-scale control of dengue and VL are not in place. For malaria, increased vector control and widespread implementation of insecticide treated bednets and artemisinin combinations, in parallel with strengthening of health systems and improved case management is leading to reductions in malaria among young children and pregnant

women.[18] Four countries have been certified as malaria-free in the past five years – Armenia, Morocco, Turkmenistan, and the UAE, and 34 countries have been identified as "malaria-eliminating" where the number of cases overall has decreased by 85% between 2000 to 2010.[18] According to some investigators these international efforts have shifted the global malaria disease burden away from younger children to older children and adults, especially adult males.[18] Such efforts are also shifting the malaria burden to migrant populations, with high levels of *Plasmodium vivax* infections.[18] In parallel to these control and elimination activities international efforts are in place to conduct research and development on new tropical disease vaccines, with vaccines for hookworm infection, schistosomiasis, and malaria in clinical trials.[47] However, vaccines are not widely incorporated yet into global elimination strategies alongside mass drug treatments and bednets.

Finally, in the US there is not yet widespread acknowledgement or recognition of the tropical disease problem in the southern part of the country. Ironically, we are further ahead of tropical disease control and elimination efforts internationally than we are for the US.[42,48]

While some important successes have been achieved in terms of scaling up mass drug administration for childhood helminth infections, ie, STH infections and schistosomiasis, and advancing malaria elimination in some countries, there is not yet in place an overarching policy that fully integrates all of the major pediatric tropical diseases. Yet, in Africa, Asia, and elsewhere there is enormous geographic overlap between the childhood helminth infections and trachoma with the vector-borne tropical diseases such as dengue and malaria. Beyond geographic overlap, co-infections with helminthiases and vector-borne tropical diseases are common, in some cases leading to additive or possibly even synergistic morbidities. Therefore, a focused international effort should be implemented to identify both theoretical and operational mechanisms that link prevention efforts for all of the major pediatric tropical diseases and, ultimately, for integrating global control and elimination for these conditions. A series of stakeholder meetings led by the WHO and their regional offices would represent an important first step for global integration of pediatric tropical disease control. Simultaneously, we urgently need a policy for scaling up surveillance efforts for tropical diseases in southern US, and implementing a new policy for these diseases.

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